Circadian, ultradian, and episodic gonadotropin and prolactin secretion in human pseudocyesis

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Abstract. Six women with pseudocyesis were studied by 15-min blood sampling for 12 to 24 h to determine their gonadotropin and PRL secretory profiles aiming to clarify the endocrine alterations in this form of hypothalamic amenorrhea. Clinical and biochemical evidence of hyperandrogenism was found in 4 patients. Persistent hyperprolactinemia was present only in one patient. Significant circadian and ultradian periodicities were identified by time series analysis in the 12-24 h profiles of FSH, LH and PRL secretion. Pulse analysis by the Van Cauter (ULTRA.JN) method revealed a 24-h mean LH interpulse interval of 91±21 min with a mean LH amplitude of 5.4±0.8 IU/l. There was a significantly lower pulse frequency at night than during the daytime. The mean 24-h PRL interpulse interval and pulse amplitude were 134±22 min and 9.2±1.8 IU/l, respectively. Both FSH and LH mean levels were higher during the daytime than at night, while the reverse was true for PRL values. Decreased LH pulse frequency and amplitude emerged as the most distinctive findings. Antecedent hypothalamic-pituitary aberrations due to other endocrinopathies and the timing of the hormonal assessment (e.g. recovery phase) may explain, at least in part, the reported heterogeneity of neuroendocrinologic findings in pseudocyesis.

Pseudocyesis, or imaginary pregnancy, together with anorexia nervosa represent the more obvious examples of psychogenic amenorrhea. Although it is clear that a strong desire for or fear of pregnancy leads to the loss of menses and pregnancy-like manifestations characteristic of pseudocyesis, there is a large but conflicting literature in relation to its neuroendocrine alterations. Basal circulating levels of gonadotropins have been reported to be low, normal or high (1-6). Similarly, basal serum PRL levels have been found elevated or within normal limits (1-6). However, an exaggerated PRL response to TRH appears to be a common finding in patients with pseudocyesis (1-4). Likewise, an exaggerated LH response to GnRH has been reported (1,4). Investigation of pulsatile hormone release has been limited to a few cases (2,5,7). Moreover, with one exception (7), the restricted time period of blood sampling in these studies precludes reaching definitive conclusions.

The aim of the present study was to define further the neuroendocrine alterations in pseudocyesis by investigating the episodic release of FSH, LH and PRL in a group of patients selected by strict diagnostic criteria.

Patients and Methods
The study population consisted of 6 women aged 19 to 35 (median 22) years. All of them were amenorrheic for more than three months and exhibited a firm conviction of being pregnant despite having been informed that their pregnancy tests (including undetectable serum CG) were negative. Patients with a psychiatric condition that precluded informed consent were deemed ineligible for participation. In addition to the absolute requisites of amenorrhea and pregnancy conviction, acceptance into the study further required a score above the threshold value on a weighted pseudocyesis scoring system which we developed (Table 1). The study was performed in ac-
Table 1.
Weighted pseudocyesis scoring system. Requirements for diagnosis include a firm conviction of pregnancy, amenorrhea >3 months, undetectable serum CG, PLUS a score of >5 points:

<table>
<thead>
<tr>
<th>Manifestation</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Galactorrhea</td>
<td>1</td>
</tr>
<tr>
<td>2. Breast changes</td>
<td>1</td>
</tr>
<tr>
<td>(↑ bra size, mastodinia or fullness)</td>
<td></td>
</tr>
<tr>
<td>3. Nausea and/or vomiting</td>
<td>1</td>
</tr>
<tr>
<td>4. Weight gain (&gt;5 kg)</td>
<td>1</td>
</tr>
<tr>
<td>5. Abdominal changes</td>
<td>1</td>
</tr>
<tr>
<td>(↑ girth, bloating or distention)</td>
<td></td>
</tr>
<tr>
<td>6. Hyperpigmentation</td>
<td>1</td>
</tr>
<tr>
<td>7. &quot;Fetal movement&quot;</td>
<td>2</td>
</tr>
<tr>
<td>8. &quot;Labour pains&quot;</td>
<td>3</td>
</tr>
</tbody>
</table>

cordance with the principles of the Declaration II of Helsinki and informed consent was obtained from all patients.

Of the 6 women who qualified, two were parous with living children (E.F), while 4 were nulligravidae. All patients belonged to the low socioeconomic group. No patient engaged in regular exercise or received any hormonal or psychotropic medications in the three months prior to study. Preliminary evaluation included a complete history, physical examination and laboratory tests (blood count, urinalysis, blood chemistry including liver enzyme testing and serum CG determination) to assure good general health, as well as an interview by a clinical psychologist.

The study was conducted in a quiet room. Patients were allowed to either sit or recline without napping during the day. Smoking was prohibited. Since sleep was recorded by trained observers throughout the night, rather than monitored electroencephalographically the terms “asleep” or apparently asleep are used. Bathroom privileges were allowed. Low protein, caffeine-free meals were provided and their timing was recorded. Only staff members directly involved in the study protocol were allowed verbal contact with the patients and no visitors were permitted during the study period. Immediately after this was completed, an abdominal-pelvic ultrasound scanning was performed to reinforce the absence of pregnancy to the patient.

Blood samples were collected via a heparinized indwelling brachial IV catheter every 15 min for 11.25 to 12 h in two patients (C,E) and a 24-h period in the other four. Samples were spun and the serum frozen at −20°C until assayed.

Protein hormone determinations were obtained by RIA using commercial double-antibody kits (Diagnostic Products Corporation, Los Angeles, CA). The sensitivities of the assays of FSH, LH and PRL, were 1.2 IU/l, 2.0 IU/l and 2.0 μg/l, respectively. Each assay run included all samples from a given patient, as well as three serum pools employed to estimate intra- and inter-assay variability at different hormone concentration levels. The intra-assay coefficients of variation at low, medium and high concentration levels were as follows (all expressed in per cent): FSH: 8.1, 5.4 and 5.1; LH: 11.7, 5.4 and 3.9; and PRL: 11.6, 8.7 and 4.7. The inter-assay coefficients of variation were (all expressed in per cent): FSH: 9.4, 5.6 and 5.3; LH: 12.0, 9.0 and 8.2; and PRL: 16.2, 14.8 and 6.6 for low, medium and high hormone concentrations, respectively. For each patient a pooled sample was obtained from equal aliquots of samples obtained near 08.00 h, 16.00 h and 24.00 h for estradiol-17β (E2), progesterone, 17-hydroxyprogesterone, testosterone and sex hormone binding globulin (SHBG) determinations, and free androgen index (FAI) was calculated. These steroid hormones were assayed also by RIA in duplicate employing methods previously described (8-10). The normal early follicular phase serum values for adult women for each of the hormones are E2: 70-260 pmol/l; progesterone: <2.8 nmol/l; 17-hydroxyprogesterone: <2.4 nmol/l; testosterone: 0.5-2.2 nmol/l; SHBG: 25-121 nlmol/l, (7±4.3 nmol/l); and FAI: 2.9±0.14 per cent (10,11).

Since 24-h hormone profiles may contain both circadian (about 24 h cycles) and ultradian (periodicities of <24 h in duration) rhythms, as well as episodic secretory events (discrete surges or spikes), each hormone profile was subjected to both time series analysis (spectral analysis) and pulse analysis (12-14). To evaluate the circadian and other slow wave components, if any, of the individual hormone profiles, data characterization began with a detailed analysis of baseline variation. Repeated periodogram calculations were performed, following determination of data autocorrelation within subjects. Slow-wave frequencies which contributed significantly (p<0.05) to the total observed variance of a hormone profile were recorded. The analysis of pulsatile hormone secretion was performed by two methods. First, the method of Santen & Bardin (13) defines a pulse as an increment of serum levels of hormone which exceeds the previous nadir by 20 per cent or more. For gonadotropin pulses, this increment must also be greater than 1 IU/l. FSH pulses are indicated on the graphs as identified by both the Santen & Bardin and the ULTRA methods, however, FSH pulsatility cannot be evaluated reliably due to its long half-time and low amplitude pulsations. Although the Santen & Bardin method does not address PRL pulse analysis per se, we applied it using a minimum increment of 1 μg/l. Pulse frequency refers to the number of hormone secretory spikes or pulses detected during the 12-24 h blood sampling period. Interpulse interval, the reciprocal of pulse frequency, was determined by dividing the total
duration of the study in minutes by the number of pulses identified. Pulse amplitude is the arithmetic difference between the peak value and its preceding nadir value. Secondly, data was analysed by the ULTRA.JN computer algorithm of Van Cauter (14,15) which eliminates all increments and decrements which fail to exceed a certain threshold. Threshold values are determined by the product of a linearly interpolated value for the local coefficient of variation (CV) of the assay times and a user designated integer (e.g.: 2 or 3 times the local CV). Following an iterative process, in the final "clean series" all local "maxima" represent the peaks of significant pulses. For the gonadotropin and PRL episodic secretion analysis, we used three and two times the CV, respectively, as the threshold determinants to attain minimal false positive pulse identifications without introducing an unacceptably high false negative error.

The PRL response to lunch and dinner was assessed by comparing the mean of the two hormone values immediately antecedent to the meal to the succeeding 8 hormone values expressed as percentage of the premeal mean value for each subject. Awake versus apparently asleep hormone values were analysed by the Wilcoxon signed-rank test. The Spearman rank correlation coefficient was applied to define relationships between hormone variables. The integrated area under the curve (AUC) was calculated according to the trapezoid formula. Unless otherwise specified, p <0.05 was considered significant.

Results

General characteristics of patients

The patients had a mean duration of amenorrhea of 8.8±1.1 (range 5.5-12.5) months. All reported marked weight gain (15.9±3.4 kg; range 6.4-28.2). Although breast changes occurred in all patients, galactorrhea was present in only three (B, C, F). Nausea, vomiting, bloating, constipation and increased abdominal girth were common manifestations. Hyperpigmentation was reported by 4 patients. All claimed to have experienced "fetal movements" starting at 4-5 months of amenorrhea and one (patient A) reported "labour pains". Thus, pseudocyesis scores ranged from 6 to 10 (mean: 7.3±0.6) points. Hirsutism was noted in 4 patients (A, B, C, F) and two patients (A, F) had clitoromegaly.

Steroids

All individual patient results from the pooled specimens for steroid and SHBG assays are listed in Table 2. Summary calculations do not include

<table>
<thead>
<tr>
<th>Patient</th>
<th>E₂ pmol/l</th>
<th>P nmol/l</th>
<th>17OHP nmol/l</th>
<th>T nmol/l</th>
<th>SHBG nmol/l</th>
<th>FAI %</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>124</td>
<td>1.8</td>
<td>3.4</td>
<td>2.9</td>
<td>13</td>
<td>23.0</td>
</tr>
<tr>
<td>B</td>
<td>201</td>
<td>&lt;1.0</td>
<td>1.4</td>
<td>2.2</td>
<td>27</td>
<td>8.1</td>
</tr>
<tr>
<td>C</td>
<td>164</td>
<td>1.6</td>
<td>&lt;1.0</td>
<td>1.4</td>
<td>18</td>
<td>7.6</td>
</tr>
<tr>
<td>D</td>
<td>71</td>
<td>1.2</td>
<td>1.2</td>
<td>1.0</td>
<td>18</td>
<td>5.9</td>
</tr>
<tr>
<td>E</td>
<td>120</td>
<td>&lt;1.0</td>
<td>&lt;1.0</td>
<td>1.0</td>
<td>32</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Mean ± SEM 136±22 1.3±0.2 1.6±0.5 1.7±0.4 22±3.6 9.5±3.5

a As determined in pooled sera from three blood samples.
b Patient F results are excluded, see text for explanation. P=progesterone, 17OHP=17-hydroxy-progesterone, T=testosterone, SHBG=sex hormone binding globulin, and FAI=free androgen index.

patient F for the following reasons: a. both serum E₂ and progesterone level were in the luteal range; b. pelvic ultrasound 4 h after the sampling study revealed a right ovarian cyst compatible with a corpus luteum, and c. spontaneous menses occurred less than 48 h poststudy. Furthermore, in this patient, the 24-h sampling study was performed 15 days after she gave consent versus a delay of not more than two days in all other cases. One may conclude that she was in the recovery phase at the time of study and therefore, she had to be considered separately.

For E₂, progesterone and 17-hydroxyprogesterone, all patients' values, except F, fell within the early follicular range. Serum testosterone and SHBG levels and the FAIs revealed varying degrees of hyperandrogenism in patients A, B and C. Patient D had a normal total testosterone, low SHBG concentration and mildly elevated FAI, as well as the lowest E₂ level.

Pituitary hormone values

LH. The overall range of serum LH values was from below the limit of detectability (<2.0) to 23.6 IU/l (Fig. 1). In fact, almost all patients' values remained below the upper normal limit (<20 IU/l). In patient A, whose mean LH value was the highest, 15% of her results were elevated. In contrast, patients F and D had undetectable values in 49 and 9% of the samples, respectively. Consequently, although the grand mean ±SEM of samples for all patients (excluding F) was 10.4±0.3 IU/l, the indi-
individual means ± SEM ranged from 3.0±0.1 to 15.4±0.4 IU/l (Fig. 1). In each patient studied, except E who did not sleep during any part of her 12-h study, the mean awake value exceeded the mean "asleep" value. Graphically this is most evident in patients A and B and to a lesser extent, C, D and F (Figs. 1 and 4). LH secretion, expressed as integrated AUC, was at its peak during the morning-afternoon period and lowest at night (Table 3).

In the 24-h profiles (A, B, D and F) time series analysis detected a significant circadian period in all patients' LH studies. A significant 12-h period was identified also in patients B, C and F. More rapid LH rhythms were detected from the original data in 4 patients: C (240 min), D (180 and 90 min), A (50 min), and E (48 min). Following elimination of the circadian rhythm, other LH cycle lengths emerged in patients B (360 min) and D (160 min). Further, removal of the 12-h rhythm disclosed additional LH cycles in patient F (120 min) and B (96 min).

The results of the LH pulse analysis are displayed in Table 4. For the reasons previously described related to her recovery, patient F was not included in the summary calculations. Also patients C and E were excluded from some of the calculations since they were studied only for 11.25 and 12 h, respectively. The ULTRA and the Santen & Bardin methods correlated well regarding pulse amplitude assessment, but the latter tended to detect higher frequency of pulses. The highest pulse frequencies corresponded to two of the hyperandrogenic patients (A, B). The most hyperandrogenic patient (A) failed to show a nocturnal decrease of pulse frequency, whereas in patient F, with luteal steroid values, pulsatility became almost imperceptible. A significant (p<0.01) correlation was found between LH amplitude and FAI values. Thus, hyperandrogenism was associated with the higher LH amplitude values and, in other words, hypogonadotropism became more accentuated as the androgen levels declined.

FSH. Overall, the serum FSH values (Fig. 2) ranged from 3.7 to 17.3 IU/l (grand mean level 8.4±0.1). Similar to the LH data, all individual awake means exceeded the respective "asleep" means (p<0.05) yielding grand mean serum FSH levels of 8.6±0.1 vs 8.0±0.2 IU/l awake and "asleep", respectively.

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**Table 3.**

LH secretion expressed as integrated area under the curve per 24 h and at 8-h segments.

<table>
<thead>
<tr>
<th>Patient</th>
<th>LH IU/l × min × 10^5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 h total</td>
</tr>
<tr>
<td>A</td>
<td>22.1</td>
</tr>
<tr>
<td>B</td>
<td>18.6</td>
</tr>
<tr>
<td>C</td>
<td>16.5^a</td>
</tr>
<tr>
<td>D</td>
<td>5.8</td>
</tr>
<tr>
<td>E</td>
<td>9.7^a</td>
</tr>
<tr>
<td>F</td>
<td>4.3</td>
</tr>
<tr>
<td>X±SEM</td>
<td>15.5±5.0^b</td>
</tr>
</tbody>
</table>

^a Extrapolated values; patients studied for 11.25 and 12 h only. ^b Extrapolated values and patients F were excluded from the calculations (see text for explanation).
Like LH, a highly significant (p<0.01) circadian FSH rhythm was identified in all patients who completed 24-h studies (A, B, D, F). A 12-h FSH rhythm was detected in all 6 patients, however, this cycle emerged in two of them (A, D) only after the elimination of the 24-h rhythm. The lengths of other cycles detected in the original data were 8 (F) and 6 (C, E). Additional rhythms found following the removal of the circadian rhythm included 8 h (B, D) and 111 (A), 76 (D), and 46 min (F). Elimination of the 12- and 24-h rhythms disclosed more rapid cycles: of 85 (A) and 45 min (B, D).

PRL. The individual serum PRL levels ranged from a single undetectable value (<2.0) to 63.2 µg/l (Fig. 3). High daytime circulating PRL levels (>20 µg/l) were found in 3 patients (A, C, D), however, elevated values were persistent only in one. In patient C, who was studied between 01.45 and 13.00 h, 18% of her serum PRL levels were over 20 µg/l. Individual mean 24-h PRL levels ranged from 6.6±0.3 to 22.8±0.5 µg/l (Table 5). The grand mean serum PRL level was 13.6±0.4 µg/l with a lower awake than asleep value (12.6±0.5 vs 15.8±0.6 µg/l). Patients A, B, C and F exhibited the typical nocturnal increase in PRL secretion (Figs. 3 and 4). The 24-h PRL profile in patient D was most unusual. Following spontaneous awaking at 04.25 h and again at 07.50 h, she had dramatic increases in serum PRL levels (up to 62.4 and 63.2 µg/l, respectively).

A circadian PRL rhythm was discernible in all 4 patients studied for 24 h (A, B, D, F), while a 12-h one was identified in the whole group. Analysis of the original data detected also 6-h (A, B, C), 288-min (B), and 240- and 180-min (D) rhythms. Exclusion of the 24-h rhythm unmasked 288-(D), 240-(F), 206-(D), and 180-(A) min cycles. Further elimination of the 12-h rhythm allowed the identification of 360-(F), 288-(A, F) and 206-(F) min cycles. As shown in Table 5 and Fig. 3, there was a wide range of variability regarding mean PRL interpulse intervals, as well as mean PRL pulse amplitude. Serum PRL levels increased significantly after lunch and dinner, reaching peak levels at 60 min post-meals (Mean ± SEM increment: 56±5%).

### Table 4.
LH pulse analysis according to Santen & Bardin (SB) and Van Cauter (ULTRA) methods.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Interpulse intervals min</th>
<th>Pulse amplitude IU/l</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 h</td>
<td>06.00-24.00 h</td>
</tr>
<tr>
<td></td>
<td>SB</td>
<td>ULTRA</td>
</tr>
<tr>
<td>A</td>
<td>55</td>
<td>58</td>
</tr>
<tr>
<td>B</td>
<td>72</td>
<td>85</td>
</tr>
<tr>
<td>C*</td>
<td>86</td>
<td>115</td>
</tr>
<tr>
<td>D</td>
<td>85</td>
<td>131</td>
</tr>
<tr>
<td>E*</td>
<td>66</td>
<td>144</td>
</tr>
<tr>
<td>F</td>
<td>96</td>
<td>112</td>
</tr>
<tr>
<td>Mean ± SEM</td>
<td>71±9(^b)</td>
<td>91±21(^b)</td>
</tr>
</tbody>
</table>

\(a\) Patients C and E were studied for 11.25 and 12 h, respectively.
\(b\) Patients A, B, D only (see text for explanation).
\(c\) Patients A, B, D, and E only.
\(d\) Patients A, B, C, and D only.
\(e\) Patients A to E only.

Discussion

Regardless of the variability in the 24-h gonadotropin secretory patterns among our patients with pseudocyesis, certain general LH secretion characteristics emerged from this study. As compared with women with normal menstrual cycles (16,17), the amplitude of LH pulses in our patients were low-normal or definitely low. There was also a tendency towards decreased LH pulse frequency and
Fig. 2. 
Serum FSH concentration patterns as determined by 15-min blood sampling in 5 women with pseudocyesis. FSH pulses are marked as identified by Santen & Bardin criteria (Δ) and by ULTRA analysis (O). ■ = meal. The mean ± SEM FSH levels for each subject are plotted at the right according to period of study as total (T), awake (W), and apparently asleep (S).

Fig. 3. 
Serum PRL concentration patterns as determined by 15-min blood sampling in 5 women with pseudocyesis. PRL pulses are marked as identified by Santen & Bardin criteria (Δ) and by ULTRA analysis (O). ■ = meal. The mean ± SEM PRL levels for each subject are plotted at the right according to period of study as total (T), awake (W), and apparently asleep (S).

this slowdown was particularly striking at nighttime. This bimodal profile resembles the normal early follicular phase LH pulsatility pattern (16,17). Also, the mean LH AUC values in our patients with pseudocyesis were lower than those found by Berga et al. (18) in normal women during the early follicular phase, but higher than in patients with "functional hypothalamic amenorrhea". The fact that the mean LH AUC values were higher in the patients with pseudocyesis than in those with "functional hypothalamic amenorrhea" may be explained by the associated hyperandrogenism. Secretion of FSH also displayed an episodic pattern comparable to that seen during the follicular phase of the menstrual cycle. According to the classification of gonadotropin pulsatility abnormalities by Santoro et al. (19), our patients belong to the disorders of amplitude category. Diminished LH pulse amplitude has been found in patients with idiopathic hypogonadotropic hypogonadism and "hypothalamic amenorrhea associated with weight loss" (19). It should be noted that only one of the two hyperandrogenic patients with pseudocyesis studied by Starkman et al. (7) fits in this classification group. Their other patient disclosed high amplitude LH activity similar to that found in women with polycystic ovary syndrome (20, 21).

Time series analysis revealed 24- and 12-h gonadotropin rhythms in all patients. However, ultradian FSH and LH periodicities were detected rather inconsistently among them. Although this paucity may be interpreted as an inherent rhythm alteration in pseudocyesis, it may also be the result of a methodological limitation. As shown by others
(22), some LH secretory periodicities become apparent only when the rate of blood sampling is intensified. Interpretation of these data is, however, hampered by lack of appropriate normative data in women.

The normal nyctohemoral rhythm of PRL secretion was preserved in pseudocyesis. Our patients, like those of Starkman et al. (7) showed greater release of PRL at night than during daytime. In spite of a number of high individual PRL values, mean awake and "asleep" PRL levels in our patients with pseudocyesis were similar to those found in normal women (23,24). Episodic PRL release frequency, as well as pulse amplitude, appear to be higher in women with pseudocyesis than in normal men (25,26). Whether pulse frequency and amplitude are comparable in patients with pseudocyesis and hyperprolactinemia (27) is difficult to ascertain because of methodological differences. Like in normal men (26), ultradian PRL periodicities were also found in our patients. It is uncertain whether the longer ultradian periodicities detected in pseudocyesis than in normal men (180-360 min vs 22-242 min) may be attributable to gender or methodological differences, or represent an inherent pathophysiological feature. As suggested by Veldhuis & Johnson (26), harmonic values of these rapid ultradian events may translate into the lower frequency rhythms, however, their physiological significance remains unknown.

Although we studied a relatively large group of patients and used a weighted pseudocyesis scoring system to maximize homogeneity of the study population, it is readily apparent that conflicting endocrinologic findings are unavoidable. Clinical and biochemical data indicated varying degrees of hyperandrogenism in 4 of the 6 patients studied. Similar manifestations compatible with polycystic ovary
syndrome were also present in patients with pseudocyesis reported by others (2,5,7). Although hyperprolactinemia has been a relatively frequent finding in pseudocyesis (1,2,5), only one of our patients showed persistent high PRL levels. Elevation of circulating progesterone levels compatible with luteal function was evident in one of our patients and similar findings have been reported by some authors (1,2,5) but not by others (3,4,7). All these hormonal discrepancies raise the question whether neuroendocrine disturbances in patients with pseudocyesis are primarily related to an antecedent endocrinopathy. The significant correlation between LH pulse amplitude and free androgen index values gives support to this contention. This is particularly exemplified by patient A in the present study who had oligomenorrhea since menarche and was virilized. Therefore, she had pre-existing, longstanding manifestations compatible with polycystic ovary disease. Not surprisingly she exhibited the greatest LH pulse frequency and amplitude, her secretory pattern resembling that of the hyperandrogenic patient studied by Starkman et al. (7). Since the patients who had no evidence of hyperandrogenism in our study were the ones displaying less LH secretory activity, it appears that LH pulsations of low amplitude and low frequency may represent the characteristic secretory pattern of "pure" pseudocyesis. Superimposition of pseudocyesis upon pre-existent conditions such as hyperandrogenism, hyperprolactinemia or perimenopause could modify their distinctive alterations in gonadotropin secretory activity.

The timing of the endocrine assessment also may have some bearing in regards to the variation of gonadotropin secretory activity, and thereby be responsible for some of the conflicting reported hormone results. Serial studies in women with "hypothalamic amenorrhea" revealed changing patterns in LH pulsatility over time (19). Similarly, it was long ago recognized that women with anorexia nervosa display a different gonadotropin pulsatility pattern during the recovery phase, that is at the return of body weight to normal, than during the acute phase (28). It is possible that one of our patients (F) was tested during the recovery phase. Her serum progesterone and estradiol concentrations were within the normal luteal range, and she menstruated 48 h after completion of the study. These findings raise the possibility of an evolving resolution phase associated with ovulation. Clinical and hormonal data from the case of pseudocyesis reported by Yen et al. (5) suggests that it might also have been studied during the periovulatory period of her recovery. Superimposed endocrine effects of recovery may also influence, therefore, the hypothalamic-pituitary secretory activity associated with pseudocyesis. Conversely, the intrinsic hypothalamic-pituitary secretion alterations of pseudocyesis may modify the expected gonadotropin pulsatile pattern in the first few menstrual cycles of the recovery period. For example, the typical luteal high amplitude LH pulses were not apparent in our patient F in spite of luteal progesterone concentrations.

One may conclude that the use of a strict diagnostic scoring system allowed us to characterize further the spectrum of pulsatile gonadotropin and PRL secretion in pseudocyesis. It is apparent that the underlying cyclical LH aberration corresponds to the group of disorders of amplitude as classified by Santoro et al. (19), an alteration found also in other hypothalamic disturbances. Furthermore, it emerged clearly that a large percentage of our patients with pseudocyesis, as well as many reported in the literature, have antecedent hypothalamic-pituitary gonadal aberrations. These antecedent aberrations, together with variability in the study conditions and methods, explain the heterogeneity of neuroendocrine results reported in association with pseudocyesis. All these particularities make it difficult to define the precise mechanism(s) responsible for the disruption of normal hypothalamic-pituitary gonadotropin and prolactin secretion in women with pseudocyesis.

Acknowledgments

The authors are most grateful to Dr Eva Van Cauter for providing us with the ULTRA program, Dr Jack Lubowsky for computer assistance, Dr Richard Shindeldecker for statistical assistance, Mrs Barbara Kaminska-Eddy for technical support, and Mrs Mary Lombardo for secretarial assistance.

References


Received April 9th, 1990.
Accepted August 14th, 1990.

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